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(54) Title: CONTINUOUS DELIVERY OF LUTEINIZING HORMONE RELEASING HORMONE COMPOSITIONS IN COMBINATION WITH SEX STEROID DELIVERY FOR USE IN TREATING BENIGN OVARIAN SECRETORY DISORDERS (57) Abstract This invention is directed to a delivery system and a method useful for the treatment of benign ovarian secretory disorders in female mammals by administering an LHRH composition. The method comprises administering during the entire follicular phase of the menstrual cycle, beginning at the time of menses, an LHRH composition and sufficient levels of an estrogenic steroid to counteract the possibility of side effects which may develop during prolonged therapy with LHRH. Following the follicular phase, at the beginning of the luteal phase, and for the entire course of the luteal phase, the LHRH/estrogenic steroid combination administered during the follicular phase, in combination with a physiological amount of progestational steroid, is administered.		

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TITLE OF THE INVENTION

CONTINUOUS DELIVERY OF LUTEINIZING
HORMONE RELEASING HORMONE
COMPOSITIONS IN COMBINATION WITH SEX
STEROID DELIVERY FOR USE IN TREATING
BENIGN OVARIAN SECRETORY DISORDERS

FIELD OF THE INVENTION

This invention relates to therapeutic methods for the treatment of benign ovarian secretory disorders in female mammals which use continuous delivery systems for the administration of LHRH compositions, in combination with sex steroids.

BACKGROUND OF THE INVENTION

Luteinizing hormone releasing hormone (LHRH), also referred to as gonadotropin releasing hormone (GnRH), is produced in the hypothalamic region, and stimulates the release of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary gland. LH and FSH act on the gonads to simulate the synthesis of steroid hormones and to stimulate gamete maturation. The release of LHRH, by stimulating the release of LH and FSH, controls the reproductive cycle in mammals.

Numerous LHRH analogues, both agonistic and antagonistic, have been synthesized. The biological properties of LHRH and its analogues have recently been reviewed. Furr, B.J.A. et al., "Luteinizing Hormone-Releasing Hormone And Its Analogues: A review Of Biological Properties and Clinical Uses," J. Endocrinol. Invest. 11:535-557

(1988). Low doses of LHRH and/or its agonistic analogues can stimulate ovulation and are useful in the treatment of hypothalamic and anovulatory infertility in the female due to hypothalamic deficiency in the synthesis or release, or both, of LHRH resulting in a hypogonadal state. Additionally, these analogues stimulate spermatogenesis and androgen production in the male.

Paradoxically, larger doses of highly potent and long acting LHRH agonistic analogues have an opposite effect which blocks ovulation in the female and suppresses spermatogenesis and testosterone production in the male.

Inhibitory (antagonistic) analogues of LHRH have also been developed for contraceptive purposes, by acting as a competitive inhibitor to endogenous LHRH at the pituitary receptor site. Hall, J.E. et al., "Evidence of Differential Control of FSH and LH Secretion by Gonadotropin-Releasing Hormone (GnRH) from the Use of a GnRH Antagonist," J. Clin. Endocrin. Metabol. 67:524-531 (1988); Nillius, S.J., "Luteinizing Hormone Releasing Hormone Analogues for Contraception," Clinics in Ob. Gyn. 11:551-572 (1984); Monroe, S.E. et al., "Ablation of Folliculogenesis in Women by a Single Dose of Gonadotropin-Releasing Hormone Agonist: Significance of Time in Cycle," Fertility Sterility 43:361-368 (1985); Lemay, A.L. et al., "Inhibition of Ovulation During Discontinuous Intranasal Luteinizing Hormone-Releasing Hormone Agonist Dosing in Combination with Gestation-Induced Bleeding," Fertility and Sterility 43:868-877 (1985); Gudmundsson, J.A. et al., "Inhibition of Ovulation by Intranasal Nafarelin, A New Superactive Agonist of GnRH," Contraception 30:107-114 (1984); and Kuhl, H. et al., "Contraception with an LHRH Agonist: Effect on Gonadotropin and Steroid Secretion Patterns," Clinical Endocrin. 21:179-188 (1984).

Administration of large doses of LHRH analogues produce a selective, reversible and complete biochemical castration at the pituitary level. These LHRH analogues have had several therapeutic applications in medicine. The first of these application was their use

in treating precocious puberty. Another application was their use to suppress uterine fibroids. In addition, prostate cancer, and other hormonally sensitive cancers, such as breast cancer, endometriosis, and polycystic ovarian disease all have proven to be suppressed during LHRH analogue administration. Filicori, M. et al., "A Conservative Approach to the Management of Uterine Leiomyoma: Pituitary Desentiation by an LHRH Analogue," Am. J. Ob. Gyn. 6:726 (1983); Lemay, H. et al., "Reversible Hypogonadism Induced by a Luteinizing Hormone Releasing Hormone (LHRH) Agonist (Buserelin) as a New Therapeutic Approach for Endometriosis," Fertil. Steril. 41:863; Schriock, E. et al., "Treatment of Endometriosis with a Potent Agonist of Gonadotropin-Releasing Hormone (Nafarelin)," Fertil. Steril. 44:583; Chang, R.J. et al., "Steroid Secretors in Polycystic Ovarian Disease after Ovarian Suppression by a Long-Acting Gonadotropin-Releasing Hormone Agonist," J. Chem. Endomet. Metab. 56:897 (1983); Crowley, W.F. et al., J. Clin. Endocrinol. Metab. 52:370-372 (1981); and Comite, F. et al., N. Eng. J. Med. 305: 1546 (1981). The clinical uses of LHRH and its analogues have recently been reviewed. Furr, B.J.A. et al., "Luteinizing Hormone-Releasing Hormone And Its Analogues: A review Of Biological Properties and Clinical Uses," J. Endocrinol. Invest. 11:535-557 (1988); and, McLachlan, R.I. et al., "Clinical Aspects of LHRH Analogues in Gynaecology: A Review," Brit. J. Obstet. Gynecol. 93:431-454 (1986).

The central problem now emerging with this prolonged treatment relates to the nearly total biochemical castration produced by these LHRH analogues. The pituitary quiescence induced by LHRH analogues results in a total suppression of gonadotropins and ovarian steroid secretions (estradiol and progesterone). This pituitary quiescence in women leads to the side effects of estrogen deficiency, including hot flashes, vaginal dryness, and, most ominously, the possibility of osteopenia and osteoporosis. These side effects seen with prolonged LHRH therapy are thus comparable to those seen in menopausal women with a similar degree of estrogen deficiency.

EP 136,781 describes the use of LHRH agonists for the treatment of endometriosis in combination with a progestational agent. However, it would be desirable to have a treatment for benign ovarian secretory disorders which uses LHRH and/or its analogues (either agonists and/or antagonists) that can be administered in a safe, physiologic, and convenient mechanism, without the side effects relating to deprivation of the sex steroid hormones.

U.S. 4,762,717 discloses a delivery system for the continuous delivery of LHRH compositions in combination with sex steroid for use as a contraceptive. However, it has not previously been known that such delivery systems would also be useful in the treatment of benign ovarian secretory disorders.

SUMMARY OF THE INVENTION

This invention is directed to a method for treating benign ovarian secretory disorders in mammals by administration of luteinizing hormone releasing hormone (LHRH), LHRH analogues, LHRH agonists, and/or LHRH antagonists in a first delivery system which is combined with continuous administration of an effective amount of estrogenic steroids during an induced follicular phase of the menstrual cycle, beginning, if possible, at the onset of menses. After an appropriate period of time so as to simulate a normal menstrual cycle, a second delivery system is administered to simulate the luteal phase of the menstrual cycle. This second delivery system comprises the LHRH/estrogenic steroid combination, as described above, and additionally provides an effective dosage of a progestational steroid. Withdrawal of the second delivery system, most preferably by readministration of the first delivery system, results in the onset of menses.

This method provides continuous suppression of pituitary gonadotropin secretion by sequential administration of LHRH, LHRH analogues, LHRH agonists and/or LHRH antagonists, thus inhibiting

ovulation. Further, this invention permits the sequential application of estrogenic and progestational sex steroids in a sequence designed to mimic the physiologic secretions of steroids in the menstrual cycle. By this invention, the side effects of prolonged LHRH therapy resulting from indirectly induced estrogen deficiency are avoided.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

This invention is directed to a method for treatment of benign ovarian secretory disorders in mammals comprising administration through a first delivery system of an effective amount of luteinizing hormone releasing hormone (LHRH), LHRH analogues, LHRH agonists and/or LHRH antagonists, hereinafter referred to as "LHRH compositions," and an effective amount of an estrogenic steroid during an induced follicular phase of the menstrual cycle, beginning, if possible, at the onset of menses. The method then comprises replacing the first delivery system with a second delivery system. The second delivery system administers an LHRH composition, an effective dosage of estrogenic steroid, and an effective dosage of progestational steroid to the female so as to simulate a luteal phase of the menstrual cycle. Following the administration of the second delivery system, preferably the first delivery system is readministered, at which time menstruation would typically occur. The two delivery systems are thus sequentially administered at approximately the beginning of an induced follicular phase and at approximately the beginning of an induced luteal phase of the menstrual cycle.

In patients whose benign ovarian secretory disorder is characterized by amenorrhea, the methods of the invention may be initiated at any time.

The preferred delivery systems are described in U.S. 4,762,717, incorporated herein by reference.

By patient is meant a human or other animal, in which it is desired to provide medical treatment so as to control ovarian

secretion.

By simulating or inducing the follicular or luteal phase of the menstrual cycle is meant to simulate or induce the sex steroid hormone milieu in the patient so as to provide such patient with levels of sex steroid hormones that approximate the endocrine environment of a normal follicular or luteal phase.

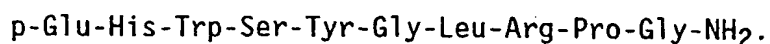
"Benign ovarian secretory disorders" as used herein refers to any of a variety of benign conditions in which suppression of ovarian function is important. These conditions largely center around benign secretory disorders of the ovaries such as a) polycystic ovarian disease and hyperandrogenic hirsutism and/or b) excessive ovarian sex steroid secretion of androgens, estrogens or progestins.

By "excessive" ovarian sex steroid secretion of androgens, estrogens or progestins is meant secretion of androgens, estrogens or progestins in amounts such that the ratios of the androgens, estrogens or progestins in the serum of a patient are abnormal when compared to normal levels of such androgens, estrogens or progestins for the female mammal. Therefore, "excessive" estrogen secretion is meant to encompass conditions wherein the ovaries secrete too much estrogen; "excessive" progestin secretion is meant to encompass conditions wherein the ovaries secrete too much progestin; and, "excessive" androgen secretion is meant to encompass conditions wherein the ovaries secrete too much androgen.

In addition, patients with disorders such that their ovaries malfunction for any of a variety of reasons such that their ovaries secrete excessive sex steroids, i.e., estrogens, progestins, and/or androgens, the consequences of which are recurrent irregular menstrual periods, and/or hirsutism would be included in the methods of the invention. Especially, the methods of the invention are useful in treating polycystic ovarian disease, and ovarian diseases characterized by dysfunctional uterine bleeding, amenorrhea, and especially hyper-, normo-, or hypo-gonadotropic amenorrhea, and hyperthecosis.

The methods of the invention are characterized in that they provide a continuous hormonal replacement therapy which simulates a normal sex steroid hormone pattern in the patient.

"LHRH composition" is used herein to describe luteinizing hormone releasing hormone (LHRH), LHRH analogues, LHRH agonists and LHRH antagonists. The LHRH compositions that may be used in this invention are physiologically active peptides and are gonadotropin secretory inhibitors or gonadotropin-effect blockers. LHRH is characterized as a decapeptide having the following structure:



LHRH agonist and LHRH antagonist refer to such physiologically active peptides which respectively enhance or inhibit the biological activity of LHRH. For example, LHRH agonists useful in the methods of the invention include, but are not limited to, Cystorelin (Hoechst), Gonadorelin (Ayerst), ZoladexTM (ICI), Buserelin (Boechst), Leuprolide (Abbott/Takeda), Decapeptyl (Debiopharm, Ipsen/Beaufour), Nafarelin (Syntex), Lutrelin (Wyeth) and Histrelin (Ortho). LHRH, LHRH analogues, LHRH agonists and LHRH antagonists are well known in the art and are described in numerous patents, including the following patents: U.S. Pat. Nos. 4,705,778, 4,690,916, 4,530,920; 4,481,190; 4,419,347; 4,341,767; 4,318,905; 4,234,571; 4,386,074; 4,244,946; 4,218,439; 4,215,038; 4,072,668; 4,431,635; 4,317,815; 4,010,125; 4,504,414; 4,493,934; 4,377,515; 4,504,414; 4,338,305; 4,089,946; 4,111,923; 4,512,923; 4,008,209; and 4,010,149, all incorporated herein by reference. The LHRH compositions described in the above patents may be used in the methods of this invention.

As used herein, estrogenic and progestational steroids refer to both the natural and synthetic compositions for these sex steroids. These hormones are well known in the art and are described in Remington's Pharmaceutical Sciences (16th edition, 1980) at pages 925-939.

Estrogenic steroids which can be used according to the invention described herein include natural estrogenic hormones and congeners, including, but not limited to, estradiol, estradiol benzoate, estradiol cypionate, estradiol valerate, estrone, piperazine estrone sulfate, ethinyl estradiol, polyestradiol phosphate, estriol, and estrone potassium sulfate. Synthetic estrogens can be used in the invention, including, but not limited to, benzestrol, chlorotrianisene, dienestrol, diethystilbestrol, diethylstilbestrol diphosphate, and mestranol. In the preferred embodiment of this invention, natural estrogenic hormones are used.

Also included are estrogens developed for veterinary use, including equine estrogens such as equilelinin, equilelinin sulfate and estetrol.

Typical dose ranges for estrogenic steroids will depend upon the estrogenic steroid compounds chosen for use in the methods of the invention and the female mammal patient. As an example for estradiol, for the human adult female, typical dose ranges will be administered such that the serum level of estradiol will be from about 20 to about 200 pg/ml. Preferably the serum level of estradiol is from about 50 to about 150 pg/ml; more preferably from about 80 to about 120 pg/ml. Levels of the synthetic estrogens which are the physiological equivalents of these ranges of estradiol can be used according to the methods of the invention.

Progestational steroids which can be used according to the invention described herein include, but are not limited to, dydrogesterone, ethynodiol diacetate, hydroxyprogesterone caproate, medroxyprogesterone acetate, norethindrone, norethindrone acetate, norethynodrel, norgestrel, progesterone, and megestrol acetate.

Veterinarian progestational steroids can also be used in this invention, including acetoxypregesterone, chlormadinone acetate, delmadinone acetate, proligerone, melengestrol acetate, and megestrol acetate.

Typical dose ranges for progestational steroids will also depend

upon the progestational steroid chosen for use in this invention and upon the female mammal patient. For a human adult female, typical dose ranges will be an amount which can be administered such that the patient's serum levels of progesterone will be from about 1 to about 20 ng/ml. Preferably the serum level of progesterone is from about 1 to about 15 ng/ml; more preferably from about 2 to about 10 ng/ml.

In the combined administration of an effective dose of LHRH composition, the dose range will depend upon the particular LHRH composition used, but will be in an amount sufficient to suppress LH and FSH by the action of the LHRH composition on the pituitary membrane receptor. As will be understood by one of skill in the art, the effective dose ranges will be compound specific and will depend upon patient characteristics, such as species, age and weight. Further, the effective amount of LHRH composition will also depend upon the route of administration. Thus, administration by oral, subcutaneous, intramuscular, and intravenous routes will typically require less LHRH composition than administration by nasal, aural, transdermal, or vaginal routes. An effective dose range of LHRH composition may be determined by routine testing by one of skill in the art, without undue experimentation. Further, the LHRH composition may comprise one LHRH composition or may comprise two or more LHRH compositions. In general, it is expedient to administer the active LHRH composition in amounts between about 0.01 to 10 mg/kg of body weight per day. It will be understood in the art that this range will vary depending upon whether a LHRH antagonistic analogue or a LHRH agonistic analogue, or a combination of the two, is administered.

As is known in the art, menstrual cycles are characteristic of humans and primates and do not occur in other vertebrate groups. Other mammals have estrous cycles. Both menstrual cycles and estrous cycles are regulated by the same interaction of the hypothalamic, pituitary and ovarian hormones, and the effects of the ovarian hormones on the reproductive tract are comparable. The menstrual cycle is generally divided into two phases: the follicular phase and

the luteal phase. The follicular phase extends from the onset of menstruation to ovulation (approximately 14 days in the humans). The luteal phase extends from ovulation to the beginning of menstruation (approximately another 14 days in humans).

The estrous cycle is generally divided into four phases: the estrus phase, the metestrus phase, the diestrus phase, and the proestrus phase. Ovulation typically occurs during the estrus phase and thus the estrus and metestrus phases roughly correspond to the luteal phase. The diestrus phase and proestrus phase roughly correspond to the follicular phase. As used herein, these phases are all referred to as follicular and luteal phases of the menstrual cycle, although it is to be understood that the invention described herein also applies to mammals with estrous cycles. Appropriate dose ranges can be determined for mammals with estrous cycles by one of skill in the art through routine testing, without undue experimentation. In mammals with estrous cycles, it may also be desirable to control estrous behavior. The dose range administered for prevention of pregnancy and reduction of estrous behavior can also be determined by one of skill in the art by routine testing. The methods would be especially useful in treating, for example, female animals diagnosed with cystic ovarian disease (COD) and especially when such cysts manifest themselves as nymphomania, continuous estrus, irregular estrus, first estrus postpartum, anestrus since calving, anestrus after estrus, persistent corpus luteum or anestrus after insemination.

The methods of this invention may be administered to mammals including but not limited to humans, primates, equines, canines, felines, bovines, ovines, ursines, and fowl.

The first delivery system may be replaced after the second delivery system at any time in which it is desired to begin simulation of the luteal phase, for example, administration of the second delivery system so as to simulate the luteal phase may begin on a monthly, alternate monthly, or every third monthly frequency.

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LHRH compositions are absorbed very well across a wide variety of surfaces. Thus oral, subcutaneous, intramuscular, intravenous, vaginal, nasal, transdermal and aural routes of administration have all proven to be effective. In one embodiment of this invention, administration of the delivery system is made via the vaginal route. Approximately 10% of the LHRH composition is absorbed through the vaginal route. Thus, the LHRH composition is administered via a vaginal delivery system using a matrix which permits slow degradation of the LHRH composition and transvaginal absorption. In this same first vaginal delivery system an effective dosage of physiological amounts of an estrogenic steroid is also delivered. This delivery system allows complete suppression of gonadotropins, removal of reproductive function of the ovaries, total suppression of ovarian steroidogenesis, and yet still effects a physiological replacement of sufficient levels of estrogen to thwart the long term side effects of LHRH administration. This first vaginal delivery system is administered during the follicular phase of the menstrual cycle, beginning at the onset of menses.

The methods of the invention would also be useful in to induce breeding. In seasonal breeding animals, for example sheep, sequential application of an induced follicular phase of variably length followed by an induced luteal phase would induce subsequent estrous. Such induced estrous provides a more timely and experimentally controllable breeding. The methods of the invention would also serve to induce breeding at a higher frequency, for example, to induce breeding more than once or twice a year.

Following maintenance of the LHRH/estrogenic steroid delivery system during the follicular phase (typically fourteen days in humans), this first delivery system is replaced by a second vaginal delivery system which has the LHRH/estrogenic steroid combination and an effective physiological amount of a administered during the luteal phase of the menstrual cycle (typically fourteen days in humans), until the onset of menses. This second delivery system provides an

artificial luteal phase to the females.

Following the second vaginal delivery system, and readministration of the first vaginal delivery system, menstruation occurs, reassuring the patient of lack of conception. Further, the administration of a progestational steroid in the second delivery system permitting menstruation, also avoids endometrial hyperplasia.

The matrix carrier vehicle may be one of a known class material suitable for use with the controlled release of the foregoing compositions in the physiological environment of the vagina. Typical examples include polymeric diffusion material, such as those described in U.S. Pat. Nos. 4,012,496 and 3,854,480, incorporated herein by reference. Preferably, the matrix carrier vehicles of U.S. 4,391,797, incorporated herein by reference, are used.

The invention further comprises a delivery system comprising a first delivery system for administration to a female mammal, during an induced follicular phase of the menstrual cycle beginning, if possible, at the onset of menstruation, of an effective amount of LHRH composition and an effective amount of estrogenic steroid; and a second delivery system for administration to the female during an induced luteal phase of the menstrual cycle, of an effective amount of an LHRH composition, an effective amount of estrogenic steroid, and an effective amount of progestational steroid.

This delivery system comprises an apparatus or device for administering the LHRH composition, estrogenic steroid, and progestational steroid. Typical apparatus or devices that can be used in this invention include rings, suppositories, other surface-active devices for transvaginal administration of the compounds.

The delivery system according to this invention can also comprise a drug delivery system comprising two formulations: the first formulation comprises a LHRH composition and estrogenic steroid and the second formulation comprises a LHRH composition, an estrogenic steroid, and a progestational steroid. These formulations can be in the form of a tablet for oral administration. These formulations can

also be in the form of a suspension or aerosol for subcutaneous, intramuscular, intravenous, nasal, and aural routes of administration. For transdermal administration, it is preferred that the formulation be in the form of a cream for topical administration by which the active ingredients can be absorbed through the skin. All of the foregoing formulations may be prepared by any of the methods well known in the pharmaceutical art, for example, as described in Remington's Pharmaceutical Sciences (16th edition, 1980).

The following examples describe the materials and methods that may be used in carrying out the invention. The examples are not intended to limit the invention in any manner.

EXAMPLES

The following are summary examples of delivery systems for use with the methods of this invention, each in a sequential administration cycle.

EXAMPLE 1

An adult female human patient seeking treatment for a benign ovarian secretory disorder is provided with the following treatment:

In an induced follicular phase, the first delivery system administers an LHRH composition and a natural estrogenic steroid, such that the amount of LHRH composition suppresses LH and FSH secretion during the entire period of administration, and the serum level of estrogen is maintained at from about 20 to about 200 pg/ml.

The first delivery system is replaced after approximately 14 days, with a second delivery system, on a monthly, alternate monthly, or every third monthly frequency, so as to simulate the luteal phase.

The second delivery system administers an LHRH composition, a natural estrogenic steroid, and a progestational steroid, such that, during the entire period, the amount of LHRH composition suppresses LH and

FSH; the serum level of estradiol is maintained at from about 20 to about 200 pg/ml (or equivalent estrogenic potency by bioassay); and the serum level of progesterone is maintained at from about 1 to 10 ng/ml (or equivalent progestin potency by bioassay).

The second delivery system is removed after approximately 14 days (typically the beginning of menstruation). The first delivery system is then readministered and menstruation occurs.

Thus, there is a sequential administration of the first and second delivery system designed to inhibit ovulation while supplying sex steroids in amounts associated with physiologic levels encountered during menstrual function.

EXAMPLE 2

An adult cow which comes into estrous at intervals shorter than the shortest normal cycle of 17 days and which exhibits significantly lower concentrations of progesterone and significantly higher concentrations of estrogens (a nymphomaniac cow, Saumande, J. et al., "Estradiol 17-Beta and Progesterone in Nymphomaniac Cows," Theriogenology 12:27-32 (1979)), as compared, with a cow of the same breed, at estrous, but which has a normal estrous cycle, is provided with the following treatment:

In an induced diestrus and proestrus phases, a first delivery system is administered which provides an effective amount of a luteinizing hormone releasing hormone (LHRH) composition and an effective amount of an estrogenic steroid to said female mammal such that the amount of LHRH composition suppresses LH and FSH secretion during the entire period of administration, and the serum level of estrogen which is maintained in the cow is a level which is physiologically normal for this breed of cow; then, during simulated estrus and metestrus phases, the said first delivery system is replaced with a second delivery system, wherein said second delivery

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system administers a luteinizing hormone releasing hormone (LHRH) composition, an effective amount of an estrogenic steroid and an effective amount of a progestational steroid to said cow such that during the entire period, the amount of LHRH composition suppresses LH and FSH, and the serum levels of estrogen and progesterone which are maintained in the cow are levels which are physiologically normal for this breed of cow.

Thus, there is a sequential administration of the first and second delivery system designed to supply sex steroids in amounts associated with physiologic levels encountered during the estrous cycle such that the cow being treated now maintains an estrous cycle with a normal cycle of at least 17 days.

EXAMPLE 3

The following Table 1 shows the structure of decapeptide LHRH and some of its potent agonists and antagonists which may be administered in the delivery system described in Examples 1 and 2.

TABLE 1
Structures of LHRH and Potent Agonists and Antagonists

LHRH	Agonist			
	I	II Buserelin	III Nafarelin	IV Histrelin
Pyro-Glu	--	--	--	
His				
Trp				
Ser				
Tyr				
Gly	D-Trp	D-Ser(TBU)	D(NAL2)	D-His(imBzl)
Leu				
Arg				
Pro				
Gly-NH ₂	EA*	EA*	--	Pro-NEt

LHRH	Antagonist		
	I	II	III
Pyro-Glu	Ac- ² Δ-Pro	NAc-D-p-Cl-Phe	
His	p-F-D-Phe	NAc-D-p-Cl-Phe	D-Phe
Trp	D-Trp	D-Trp	D-Trp
Ser			
Tyr			
Gly	D-Trp	D-Phe	D-Phe
Leu			
Arg			
Pro			
Gly-NH ₂	--	D-Ala	--

*EA = des-Gly-NH₂10-ethylamide.

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The foregoing invention has been described in some detail by illustration and example for purposes of clarity and understanding. It would be obvious that certain changes and modifications may be practiced within the scope of the invention, as limited only by the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A method for the treatment of a benign ovarian secretory disorder in a female mammal, comprising:
 - (a) administering via a first delivery system an effective amount of a luteinizing hormone releasing hormone (LHRH) composition and an effective amount of an estrogenic steroid to said female mammal during an induced follicular phase; and,
 - (b) replacing said first delivery system at the end of said follicular phase with a second delivery system, wherein said second delivery system administers a luteinizing hormone releasing hormone (LHRH) composition, an effective amount of an estrogenic steroid and an effective amount of a progestational steroid to said female during a simulated luteal phase, until the beginning of menses in said female.
2. The method according to claim 1 wherein said female mammal comprises a human female.
3. A method for the treatment of a benign ovarian secretory disorder in a female mammal, comprising:
 - (a) administering via a first delivery system an effective amount of a luteinizing hormone releasing hormone (LHRH) composition and an effective amount of an estrogenic steroid to said female mammal during induced diestrus and proestrus phases; and,
 - (b) replacing said first delivery system at the end of said diestrus and proestrus phase with a second delivery system, wherein said second delivery system administers a luteinizing hormone releasing hormone (LHRH) composition, an effective amount of an estrogenic steroid and an effective amount of a progestational steroid to said female during simulated estrus and metestrus phases.
4. The method according to claim 3, wherein said female mammal

is bovine.

5. The method according to any one of claims 1 or 3, wherein said administration of said first or second delivery system is selected from the group consisting of oral, subcutaneous, intramuscular, intravenous, vaginal, nasal, transdermal or aural routes of administration.

6. The method according to any one of claims 1 or 3, wherein said route of administration is by vaginal means.

7. The method according to claim 6 wherein said vaginal means is by a vaginal ring delivery system.

8. The method according to claim 6 wherein said vaginal means is by a suppository.

9. The method according to any one of claims 1 or 3, wherein said benign ovarian secretory disorder is polycystic ovarian disease.

10. The method according to any one of claims 1 or 3, wherein said benign ovarian secretory disorder is characterized by excessive ovarian progesterone secretion.

11. The method according to any one of claims 1 or 3, wherein said benign ovarian secretory disorder is characterized by excessive ovarian estrogen secretion.

12. The method according to claim 1, wherein said benign ovarian secretory disorder is characterized by hyperthecosis.

13. The method according to claim 1, wherein said benign ovarian secretory disorder is characterized by hirsutism.

14. The method according to claim 1, wherein said benign ovarian secretory disorder is characterized by dysfunctional uterine bleeding.
15. The method according to claim 1, wherein said benign ovarian secretory disorder is characterized by amenorrhea.
16. The method according to claim 3, wherein said benign ovarian secretory disorder is characterized by anestrus.
17. A method for increasing the breeding rate of an animal, wherein said animal is induced to breed by the method of claim 3.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US90/04464

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC (5): A61K 37/36 U.S. CL. 424/422; 514/899														
II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black; margin: 5px 0;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 25%; border: 1px solid black; text-align: left; padding: 5px;">Classification System</th> <th style="border: 1px solid black; text-align: left; padding: 5px;">Classification Symbols</th> </tr> <tr> <td style="border: 1px solid black; text-align: center; padding: 10px;">U.S.</td> <td style="border: 1px solid black; padding: 10px;">424/422; 514/899</td> </tr> </table> <div style="border: 1px solid black; padding: 5px; margin-top: 5px;"> Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸ </div>			Classification System	Classification Symbols	U.S.	424/422; 514/899								
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III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; border: 1px solid black; text-align: left; padding: 5px;">Category [*]</th> <th style="border: 1px solid black; text-align: left; padding: 5px;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="border: 1px solid black; text-align: left; padding: 5px;">Relevant to Claim No. ¹³</th> </tr> </thead> <tbody> <tr> <td style="border: 1px solid black; text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="border: 1px solid black; padding: 5px;">US, A, 4,762,717 (CROWLEY, JR.) 09 AUGUST 1988; See Claims 1-13.</td> <td style="border: 1px solid black; text-align: center; vertical-align: top; padding: 5px;">1-8</td> </tr> <tr> <td style="border: 1px solid black; text-align: center; vertical-align: top; padding: 5px;">A</td> <td style="border: 1px solid black; padding: 5px;">US, A, 4,705,778 (ALMQUIST) 10 NOVEMBER 1987; See column 18, lines 3-45.</td> <td style="border: 1px solid black; text-align: center; vertical-align: top; padding: 5px;">1-8</td> </tr> <tr> <td style="border: 1px solid black; text-align: center; vertical-align: top; padding: 5px;">A,P</td> <td style="border: 1px solid black; padding: 5px;">US, A, 4,888,074 (POCKNELL) 19 DECEMBER 1989 See column 1, line 63 - column 2, line 1 and column 3, lines 49-54.</td> <td style="border: 1px solid black; text-align: center; vertical-align: top; padding: 5px;">1-8</td> </tr> </tbody> </table>			Category [*]	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	X	US, A, 4,762,717 (CROWLEY, JR.) 09 AUGUST 1988; See Claims 1-13.	1-8	A	US, A, 4,705,778 (ALMQUIST) 10 NOVEMBER 1987; See column 18, lines 3-45.	1-8	A,P	US, A, 4,888,074 (POCKNELL) 19 DECEMBER 1989 See column 1, line 63 - column 2, line 1 and column 3, lines 49-54.	1-8
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<div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p>[*] Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 48%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"Δ" document member of the same patent family</p> </div> </div>														
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border-bottom: 1px solid black; padding: 5px;"> Date of the Actual Completion of the International Search <div style="text-align: center;">26 SEPTEMBER 1990</div> </td> <td style="width: 50%; border-bottom: 1px solid black; padding: 5px;"> Date of Mailing of this International Search Report <div style="text-align: center; font-size: 1.2em;">07 JAN 1991</div> </td> </tr> <tr> <td style="border-bottom: 1px solid black; padding: 5px;"> International Searching Authority <div style="text-align: center;">ISA/US</div> </td> <td style="border-bottom: 1px solid black; padding: 5px;"> Signature of Authorized Officer <div style="text-align: center;"> Edward J. Webman </div> </td> </tr> </table>			Date of the Actual Completion of the International Search <div style="text-align: center;">26 SEPTEMBER 1990</div>	Date of Mailing of this International Search Report <div style="text-align: center; font-size: 1.2em;">07 JAN 1991</div>	International Searching Authority <div style="text-align: center;">ISA/US</div>	Signature of Authorized Officer <div style="text-align: center;"> Edward J. Webman </div>								
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